Molecular selection for 'smart' study design in lung cancer

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The ZODIAC trial reported that the addition of vandetanib to docetaxel in second-line treatment of unselected patients with metastatic non-small-cell lung cancer resulted in a statistically significant improvement in progression-free survival compared with docetaxel alone. Identification of biomarkers to assist in molecular selection of patients for targeted therapy is a tool for 'smart' clinical trial design.

Patients with advanced or metastatic non-small-cell lung cancer (NSCLC) have a dismal outcome. Platinum-based chemotherapy is the standard first-line treatment; however, this approach yields disappointing median survival rates that do not exceed one year. Molecularly targeted agents that block pivotal pathways in cancer progression and can reverse chemoresistance seem promising. EGFR inhibitors and anti-angiogenic compounds have demonstrated marginal benefit in unselected cohorts of patients with advanced NSCLC. However, the superiority of gefitinib over chemotherapy was demonstrated in a molecularly selected population of patients bearing a sensitising *EGFR* mutation.[1] Novel molecular therapies such as those targeting the insulin-like growth factor 1 receptor or the EML4–ALK fusion protein have shown promising results in preliminary studies. Other targeted therapies acting on RAS/RAF/MEK, PI3K/AKT/mTOR or MET kinase are being studied in clinical trials, especially in resistant patients.

Patients with advanced NSCLC will eventually relapse or develop resistance to first-line treatment. Several chemotherapy agents, such as docetaxel and pemetrexed, have shown activity and have been approved by the FDA for second-line treatment of advanced or metastatic NSCLC. Docetaxel is associated with response rates between 15% and 20%, overall survival of 8.3 months and one-year survival rates of up to 37%.[2] A meta-analysis that evaluated the benefit of two-drug combinations versus single-agent chemotherapy in the second-line setting and demonstrated improvements in response rates with two-drug combinations did not translate into improvements in progression-free survival (PFS) or overall survival.[3] In addition, the two-drug combinations were associated with substantial toxic effects.

A rational approach to improve activity in the second-line setting might be the combination of a targeted agent with conventional single-agent chemotherapy. Several targeted therapies have been tested in the second-line setting. Erlotinib is an EGFR tyrosine kinase inhibitor (TKI) approved for second-line therapy in NSCLC. A randomised study comparing erlotinib with placebo showed improvement in median overall survival (6.7 months vs 4.7 months) and quality of life across all patient subgroups within the erlotinib arm.[4] Gefitinib, another EGFR TKI with a different pharmacokinetic profile to erlotinib, failed to yield a

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in ***Nature Reviews Clinical Oncology*** 2010 vol.7 no.11, and is published with permission. © 2010 Nature Publishing Group. doi:10.1038/nrclinonc.2010.156, www.nature.com/nrclinonc

survival advantage in a phase III trial.[5]

A new study has reported promising results using vandetanib in combination with docetaxel to treat patients with advanced NSCLC.[6] Vandetanib is an oral inhibitor of EGFR and VEGF signalling pathways. The agent also targets the rearranged during transfection (RET) tyrosine kinase, an important growth factor in thyroid and other cancers. Vandetanib reverses primary or acquired resistance to EGFR TKIs in xenograft models of human NSCLC, particularly in resistant tumours with high tumour-derived and host-derived VEGF levels.[7] In a randomised phase III trial of second-line therapy for NSCLC, vandetanib single-agent therapy demonstrated equivalent efficacy to erlotinib, but with additional toxic effects (such as diarrhoea, hypertension and asymptomatic QTc prolongation).[8] Vandetanib improved PFS in combination with docetaxel, compared with docetaxel alone, in a randomised phase II trial.[9] An interesting subset analysis suggested the benefit was greatest for women.[9]

Herbst et al.[6] have now reported results from a randomised, double-blind, phase III study (the ZODIAC trial) to confirm the PFS benefit of adding vandetanib (100 mg) to docetaxel in advanced NSCLC. The study included 1391 patients randomly assigned to receive vandetanib 100 mg daily plus docetaxel or placebo plus docetaxel. Docetaxel could be given for up to six 75 mg/m^2 doses (or 60 mg/m^2 for patients treated in Japan) on a three-week schedule. The primary objective was a 20% improvement in PFS. The outcomes in women were also analysed independently to the whole study population.

The ZODIAC study demonstrated a very modest but significant gain in median PFS of 0.6 months (4 months with vandetanib vs 3.2 months with placebo, $P<0.0001$) and a similar PFS gain in women (from 4.2 months to 4.6 months in the placebo and vandetanib groups, respectively). Herbst and colleagues observed no improvement in overall survival, and only a 6% difference in the proportion of patients who had disease progression by six months after treatment. This small improvement in PFS occurred at a cost of substantial toxic effects; grade 3 and 4 adverse events including rash, leukopenia, neutropenia, and neutropenic fever were more common in the vandetanib group than in the placebo group, and QTc prolongation requiring dose interruption was noted in nearly 2% of patients. A longer time to deterioration of lung cancer symptoms was also reported in patients receiving vandetanib. Interestingly, the median exposure to docetaxel was only four cycles (or approximately 12 weeks) in each arm, and importantly, monotherapy with vandetanib continued in the experimental arm, while no active therapy was used in the placebo arm after discontinuation of docetaxel. A weakness of the study, as the authors point out, is that despite PFS being the primary endpoint there was no independent blinded review of radiological evaluations.

A phase III comparison of pemetrexed plus vandetanib versus pemetrexed alone in previously treated patients with NSCLC (the ZEAL trial) did not meet the primary endpoint of statistically significant PFS prolongation.[10] Similar to the ZODIAC trial, the ZEAL study demonstrated a significantly higher overall response rate and symptom control in the vandetanib group compared with pemetrexed alone.

The increase in PFS of borderline clinical significance with an increase in toxic effects and no improvement in overall survival, reported in the ZODIAC trial, taken in the context of the negative ZEAL trial, are unlikely to impact the current standard of care in patients receiving second-line treatment. For good responders to first-line chemotherapy, single-agent chemotherapy such as docetaxel or pemetrexed constitutes a rational choice with fewer toxic effects. EGFR TKI is preferred in patients with poor response or tolerance to first-line chemotherapy.

The results reported by Herbst et al.[6] underscore the vital importance of incorporation of molecular selection into the future design of clinical trials that use targeted therapies. For example, *EGFR* mutations are considered predictive biomarkers of high clinical benefit with EGFR TKI therapy, especially for first-line treatment. Herbst and co-workers did not present a subgroup analysis of tumour and circulating biomarker data including *EGFR* mutation status, as the analysis is still ongoing. Inhibition of VEGF and RET signaling may have also contributed to the antitumour efficacy of vandetanib.

A personalised approach to treatment selection is the future of lung cancer management in all lines of therapy. Such an approach may require tumour re-biopsy before administration of second-line therapy to identify, for example, known biomarkers of resistance to EGFR TKI. Noninvasive approaches, such as biomarker analysis on circulating tumour cells and blood biomarkers predictive of response or resistance, hold promise for treatment selection. Unfortunately, for most targeted therapies, clinically validated biomarkers have not been identified, and this remains a critical focus of research in the field.

Practice points

- The combination of a chemotherapy drug and a molecular-targeted agent appears to be a rational approach for previously treated patients with advanced NSCLC; however, clinical trials in un-selected patient cohorts often fail to demonstrate substantial survival benefit.
- Identification and validation of biomarkers for response or resistance will assist in the development of personalised targeted strategies in advanced NSCLC.

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